## REMARKS

Claims 1-20 are pending in this application. Claims 2, 4, 8, 9, and 12-20 have been withdrawn as being directed to a non-elected invention. Claims 10 and 11 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Claims 1, 3, 5-7, 10 and 11 are rejected under 35 U.S.C. § 103(a) for obviousness over Deboer (U.S. Patent No. 5,633,076; hereinafter "Deboer"), Clark (U.S. Patent No. 5,32,775; hereinafter "Clark"), or Lubon (U.S. Patent No. 5,831,141; hereinafter "Lubon") in view of Morinaga et al. (PNAS 80:4604-4608; 1983; hereinafter "Morinaga") and Bennett (Breast Cancer Res. Treatment 45:169-179, 1997; hereinafter "Bennett"). By this reply, Applicants cancel claims 3, 5, 10, and 11, add new claims 21-24, and address each of the Examiner's rejections.

### Support for the Amendment

Applicants have added new claims 21-24. Support for new claims 21 and 22 is found in prior claims 3 and 5. Support for new claims 23 and 24 is found in prior claims 10 and 11, and in the specification at, e.g., page 15, line 4, through page 16, line 1. No new matter is added by the amendment.

### Telephone Interview with the Examiner

Applicants wish to thank the Examiner for the telephonic interview of November 8, 2006. Based on the discussion with the Examiner, Applicants believe that the present amendments and the remarks below address all of the issues raised by the Examiner in the present Office Action and place the claims in conditions for allowance. If the Examiner does not agree, Applicants respectfully request that the Examiner contact the undersigned by phone in order to resolve any remaining issues in this case.

### Rejections under 35 U.S.C. § 112, first paragraph

Claims 10 and 11 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. Applicants have cancelled claims 10 and 11. Thus, this rejection can now be withdrawn.

Rejections under 35 U.S.C. § 103

Claims 1, 3, 5-7, 10, and 11 are rejected under 35 U.S.C. § 103(a) for obviousness over Deboer, Clark, or Lubon in view of Morinaga and Bennett. The Examiner states:

> Bennett provides support for an art-recognized need to produce large quantities of rHuAFP. That Bennett provides a means differing from that of the instant invention for obtaining such large quantities of rHuAFP does not overcome the instant rejection. Furthermore, it is noted that AFP is well-known in the art to be a glycosylated protein and it is also well-known that proteins made using bacterial expression systems like that of Bennett are not post-translationally processed...Regardless of the success of using the *E. coli* system of Bennett, one of skill in the art would be motivated to use a mammalian system to obtain post-translationally processed forms of the protein or a source of the protein that does not need to undergo solubilization and refolding steps. Thus, with Bennett demonstrating a desire for one of skill in the art to obtain large quantities of rHuAFP and Clark, as well as DeBoer and Lubon, teaching a mammalian system as a means of overcoming short-comings of a prokaryotic system in manufacturing large quantities of a protein, as exemplified by Bennett, one of skill in the [art] would clearly have been motivated to carry out the claimed invention at the time the application was filed...Thus, the claimed invention, as a whole, is clearly prima obvious in the absence of evidence to the contrary. (Office Action, pp. 5-6.)

Applicants respectfully traverse the rejection of claims 1, 3, 5-7, 10, and 11.

Applicants wish to address the points raised in the Office Action as well as the clarifying remarks by the Examiner during the telephonic interview conducted on November 8, 2006. The Examiner states that the production of recombinant human alpha-fetoprotein by any means, including by using a transgenic animal, is obvious in light of the cited art because one skilled in the art would be motivated, without an explicit teaching or suggestion in the art, to produce rHuAFP using a transgenic animal. The Examiner supports this position by stating that transgenic animals are known to produce large quantities of protein and one skilled in the art would be motivated to use any technique known in the art to achieve this result given Bennett's disclosure that large quantities of rHuAFP are desirable. Furthermore, the Examiner indicates that the skilled artisan would have been motivated to move beyond the *E. coli* system of Bennett

to obtain post-translationally glycosylated rHuAFP because native human AFP is glycosylated and because expression in a mammalian system would avoid the need to solubilize and refold rHuAFP expressed in a prokaryotic system (Office Action, p. 6 and Telephonic Interview, November 8, 2006). The Examiner's position is simply unsupported by the prior art.

As was discussed in the prior Reply to Office Action, dated April 28, 2006, Bennett expresses no dissatisfaction with the *E. coli* expression system and, in fact, unequivocally indicates that it addresses all of the problems associated with establishing sufficient quantities of rHuAFP (i.e., the therapeutic effects of AFP "can now be explored in greater depth with the availability of large quantities of functional rAFP"; see p. 178; emphasis added). Furthermore, nowhere does Bennett indicate that the absence of post-translational glycosylation due to expression in a prokaryotic system affects the biological activity of rHuAFP or diminishes its usefulness. Quite the opposite, Bennett proclaims that "for the first time large quantities of pure, homogeneous, functional rAFP will enable systematic study of [the biological function of AFP]" (see page 178, col. 1; emphasis added). Thus, contrary to the Examiner's position, Bennett clearly confirms that rHuAFP expression in *E. coli* is *preferred* and implies that other expression systems available at the time, including mammalian expression systems, are not preferred.

Moreover, again contrary to the Examiner's position, Bennett cannot be relied upon as providing motivation to express rHuAFP in a mammalian system for the purpose of providing post-translational modifications absent in the prokaryotic system. Bennett unambiguously states that expression of the non-glycosylated rHuAFP is preferred, stating that the production of rHuAFP "where it is the only human protein and [it] is in an environment where post-synthetic modifications are absent" removes difficulties in determining the activity of proteins, such as AFP (see p. 176, col. 2). Bennett simply provides no motivation to express rHuAFP in a mammalian system to obtain a post-translationally glycosylated form of rHuAFP. Given Bennett's clear preference for the *E. coli* expression system, one skilled in the art would not be motivated to pursue the expression of rHuAFP in transgenic mammals.

Finally, the Examiner states that Bennett provides motivation to expression rHuAFP in a mammalian system rather than in a prokaryotic system because expression in the mammalian system would avoid the need to solubilize and refold rHuAFP expressed in the prokaryotic

system (Office Action, p. 6, and Telephonic Interview, November 8, 2006). Bennett again fails to provide support for this basis of the Examiner's rejection because, as is discussed above, Bennett clearly conveys no dissatisfaction with the amount or quality of rHuAFP obtained using the prokaryotic system (see, e.g., p. 178 of Bennett). Bennett fails to suggest that purifying rHuAFP from bacterial inclusion bodies was any more or less difficult than purifying rHuAFP from human cord sera (i.e., the source from which Bennett obtained native human AFP). Thus, Applicants find no explicit or implicit support for the Examiner's position that Bennett provides motivation to express rHuAFP in a mammalian system rather than in a prokaryotic system based on any perceived difficulties associated with solubilizing and refolding proteins expressed in the prokaryotic system.

For all of the reasons discussed above, Applicants respectfully submit that the prior art cited by the Examiner fails to provide any motivation to produce rHuAFP in transgenic mammals. Thus, a *prima facie* case of obviousness has not been established.

The Prior Art Failed to Suggest Applicants' Invention

The first successful production of a transgenic mammal, a transgenic mouse, occurred over 25 years ago (see, e.g., Gordon et al., P.N.A.S. 77:7380-7384, 1980). This success was followed by the successful production of larger livestock mammals, including rabbits, sheep, and pigs in 1985 (see, e.g., Hammer et al., Nature 315:680-683, 1985) and cows and goats as early as 1991 (see, e.g., Krimpenfort et al., Biotechnology 9:844-847, 1991, and Ebert et al., Biotechnology 9:835-838, 1991). The U.S. Patent and Trademark Office (U.S. PTO) issued the first patent, U.S. Patent No. 4,736,866, on the production of transgenic mammals on April 12, 1988. In addition, the production of recombinant proteins in the milk of a transgenic mammal (i.e., using the transgenic mammal as a "bioreactor") was demonstrated in mice in 1987 (see, e.g., Gordon et al., Bio/Technology 5:1183-1187, 1987). This was followed by the expression of human interleukin-2 in the milk of transgenic rabbits in 1990 (see, e.g., Buhler et al., Biotechnology 8:140-143, 1990) and, in 1991, the expression of whey acidic protein (WAP) in the milk of transgenic swine (see, e.g., Wall et al., P.N.A.S. 88:1696-1700, 1991), human alpha-1-antitrypsin in the milk of transgenic sheep (see, e.g., Wright et al., Biotechnology 8:830-834,

1991), and human tissue-type plasminogen activator in the milk of transgenic goats (see, e.g., Ebert et al., Biotechnology 9:835-838, 1991). The U.S. PTO issued the first patent, U.S. Patent No. 4,873,316, on the production and secretion of an exogenous recombinant human protein into the milk of a transgenic mammal on October 10, 1989. Over this 25 year history not one reference taught or suggested the expression and secretion, specifically, of rHuAFP into the milk of a transgenic mammal. The prior art simply failed to suggest Applicants' invention, as is recited in present claims 1, 6, 7, and 21-24.

Furthermore, Applicants note that of the almost 400 scientific publications published prior to Applicants' priority date of January 9, 1999, which describe the expression and secretion of a variety of recombinant human proteins (or the potential to express these proteins) in the milk of transgenic mammals, none teaches or suggests producing a transgenic mammal capable of expressing rHuAFP in its milk, not even a transgenic mouse (see search of PubMed database using keyword search "transgenic" and "milk" and limiting the date to January 9, 1999). Typically, the expression of a human protein of interest is first "tested" in a transgenic mouse prior to expressing the protein in a transgenic livestock mammal (e.g., pigs, sheep, goats, or cows). The reason for this being that it is more time and cost effective to use a mouse model to confirm that the human protein is capable of being expressed as a transgene (i.e., to confirm that the protein is amenable to tissue-specific expression, is biologically active when expressed, and does not cause any deleterious effects due to expression of the protein in the transgenic mammal) because mice are easier to manipulate and do not require the substantial costs involved in producing larger transgenic mammals. Thus, the prior art makes clear that, in general, the first step in the production of a non-human mammal capable of expressing and secreting an exogenous, recombinant protein into milk is the production of a transgenic mouse. The successful production of a transgenic mouse validates the ability to express the exogenous protein recombinantly and to promote its secretion into milk in a biologically active form, while also establishing the feasibility of making larger transgenic mammals, e.g., transgenic livestock.

Prior to and since the priority date of the present application, no one except Applicants taught or suggested the milk-specific expression of rHuAFP in a transgenic mammal. In fact, the first instance of such a disclosure is Applicants' own work, which was published in 2004 (see

Parker et al., Protein Expr. Purif. 38:177-183, 2004). While the prior art does disclose the production of transgenic mice that express rHuAFP in a non-tissue-specific manner (see, e.g., Yamashita et al., Biochem. Biophys. Res. Comm. 191:715-720, 1993), as well as the expression of unrelated proteins in a milk-specific manner (see above), Applicants are aware of no publication other than Applicants' own work in the entire 25 year history of this technology that teaches or suggests, either prior to or even following the filing of the present application, the production of a transgenic mammal capable of expressing and secreting rHuAFP into its milk. Applicants submit that because no one prior to Applicants even hinted at the production of a transgenic mammal capable of secreting rHuAFP into its milk, the Examiner's position that the invention of present claims 1, 3, 5-7, and 10-11 is *prima facie* obvious is not tenable. The prior art demonstrates no inquiry into the production of a transgenic mammal capable of expressing and secreting rHuAFP into milk, even though, as is discussed above, the production of transgenic mice capable of non-tissue specific expression of rHuAFP is disclosed in the prior art (see e.g., Yamashita et al., *supra*). The prior art simply fails to teach or suggest making a transgenic mammal capable of secreting rHuAFP into its milk. Moreover, nothing in any of the references cited by the Examiner would suggest combining them to achieve the invention recited in present claims 1, 6, 7, and 21-24. For this reason as well, Applicants submit that the rejection of claims 1, 3, 5-7, and 10-11 under 35 U.S.C. § 103(a) for obviousness over Deboer, Clark, or Lubon in view of Morinaga and Bennett should be withdrawn and should not be applied to present claims 1, 6, 7, and 21-24.

Applicants' Species is not Obvious in View of the Entire Genus of Transgenic Mammals

The fact that a claimed species may be encompassed by a disclosed generic genus does not by itself render the claimed species obvious (*In re Baird*, 16 F.3d 380, 382, 29 USPQ2d 1550, 1552 (Fed. Cir. 1994)). In the present case, transgenic mammals expressing human proteins represents the prior art genus. As is clear from the above remarks, this genus is quite large and encompasses several species of transgenic mammals expressing a myriad of human proteins under multiple different promoters to achieve specific or non-specific expression of the proteins in various tissues. Nothing in the prior art teaches or suggests, within this exceedingly

large genus, Applicants' particular species of a transgenic mammal that expresses, under a milk-specific promoter, rHuAFP that is secreted into milk of the transgenic mammal. This fact on its own is strong evidence indicating the non-obviousness of Applicants' species (see, e.g., M.P.E.P. § 2144.08 (II)(A)(4)(a), citing *In re Deuel*, 51 F.3d 1552, 1558, 34 USPQ2d 1210, 1215 (Fed. Cir. 1995)). Applicants also emphasize that even though Applicants' species is encompassed by the prior art genus, this alone is not sufficient to establish a *prima facie* case of obviousness (see, e.g., M.P.E.P. § 2144.08 (II)).

The M.P.E.P. § 2144.08 (II)(A) states that to establish a *prima facie* case of obviousness in a genus-species situation it is essential that the Examiner find some motivation or suggestion to make the claimed invention in light of the prior art teachings. As is discussed above, the prior art fails to provide any motivation or suggestion to produce Applicants' transgenic mammal, which is capable of expressing and secreting rHuAFP into its milk. The Examiner has not identified even a single prior art reference that teaches or suggests producing the transgenic mammal recited in present claims 21-24 using the nucleic acid of present claim 1 for production of the milk of present claims 6 and 7. The Examiner has only identified prior art references that disclose the genus of transgenic mammals capable of tissue-specific or non-tissue specific expression of recombinant proteins other than rHuAFP (i.e., Deboer, Lubon, and Clark); none of these references teaches or suggests the production of a transgenic mammal capable of expressing and secreting rHuAFP into the milk of the transgenic mammal. These references have been further combined with a reference that discloses the sequence of human AFP (Morinaga) and a reference (Bennett) that discloses the desirability of producing rHuAFP in *E. coli*, which is a non-mammalian expression system. Although Applicants' species falls within the genus of transgenic mammals disclosed by the prior art, this fact alone fails to establish the obviousness of Applicants' species absent some motivation or suggestion in the prior art to guide the skilled artisan to Applicants' species. For the reasons discussed above, the motivation or suggestion necessary to make this leap is clearly missing. The mere possibility that a skilled artisan would have produced a transgenic mammal capable of expressing and secreting rHuAFP into its milk does not make the invention recited in present claims 1, 6, 7, and 21-24 obvious "'unless the prior art suggested the desirability of [such a] modification' or replacement" (see

M.P.E.P. § 2144.08 (II)(A), quoting *In re Gordon*, 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984)); *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991)). No such motivation or suggestion has been provided by the prior art in this case. For this reason as well, Applicants respectfully request that the rejection of claims 1, 3, 5-7, and 10-11 under 35 U.S.C. § 103(a) for obviousness over Deboer, Clark, or Lubon in view of Morinaga and Bennett should be withdrawn and should not be applied to present claims 1, 6, 7, and 21-24.

The Obviousness of Claims 1, 3, 5-7, and 10-11 is only Established by Impermissible Use of Hindsight Analysis

In the remarks provided above Applicants have attempted to provide the Examiner with some context surrounding Applicants' discovery. In particular, the fact that even though transgenic technology has been available for over 25 years no one taught or suggested producing Applicants' transgenic mammals, which are capable of expressing and secreting rHuAFP into their milk. This fact, coupled with the clear desirability expressed by Bennett to continue using a prokaryotic system to produce rHuAFP, suggests that the Examiner is simply engaging in impermissible hindsight analysis to establish a basis for rejecting claims 1, 3, 5-7, and 10-11 for obviousness. Applicants recognize that "[a]ny judgement [sic] on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." (see M.P.E.P. § 2145(X)(A), citing *In re McLaughlin* 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971)). In this case, Applicants believe the Examiner has not considered the totality of the evidence, as is required (see M.P.E.P. § 2144.08 (II)(A)(4)(f)) and has applied Applicants' disclosure as a guide in making the present rejection for obviousness.

As evidence of this position, Applicants again point to the Examiner's primary reference, Bennett, which expresses a clear preference for using a prokaryotic system to produce rHuAFP. Bennett provides absolutely no teaching or suggestion to employ any mammalian expression system to express rHuAFP, and certainly not a transgenic mammal as the expression system, as is

suggested by the Examiner. Skilled artisans working in the field of recombinant protein production had already spent well over 10 years perfecting expression of rHuAFP in prokaryotes, and Bennett confirms that this system successfully achieves the goal of producing large quantities of rHuAFP (see, e.g., p. 178 of Bennett). Thus, Bennett, either alone or in combination with any of the other cited references, fails to provide any suggestion or motivation to express rHuAFP, specifically, in a transgenic mammal under the control of a mammary epithelial cell-specific promoter. Such a suggestion or motivation can only be imparted to Bennett if one has the benefit of Applicants' disclosure. This is the very essence of impermissible hindsight analysis. Thus, for this reason as well the rejection of claims 1, 3, 5-7, and 10-11 for obviousness over Deboer, Clark, or Lubon in view of Morinaga and Bennett should be withdrawn and should not be applied to present claims 1, 6, 7, and 21-24.

The Examiner may argue that even if Bennett doesn't expressly suggest or motivate one skilled in the art to produce a transgenic mammal capable of expressing and secreting rHuAFP in its milk, the skilled artisan would still be motivated to make Applicants' invention recited in present claims 1, 6, 7, and 21-24 because the production of transgenic mammals capable of expressing and secreting recombinant proteins in milk, generally, was known in the art and within the capabilities of the skilled artisan. Both the United States Court of Appeals for the Federal Circuit and this Board have emphasized that unsupported statements regarding the capabilities of one skilled in the art cannot provide the requisite motivation to modify the prior art. The Examiner's summary and conclusory analysis underscores that this obviousness rejection is nothing more than prohibited hindsight reconstruction of Applicants' invention based upon the inventive teachings in Applicants' own disclosure. *See, e.g., W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1552-53 (Fed. Cir. 1983) ("To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher."), *abrogated on other grounds*, *Exxon Research & Eng'g Co. v. U.S.*, 54 U.S.P.Q.2d 1519 (Fed. Cl. 2000). Furthermore, as is discussed above, the explicit disclosure of Bennett does not lead the skilled artisan to produce rHuAFP using any system other than the prokaryotic system.

Thus, the Examiner's rejection has turned Bennett on its head – Bennett unambiguously discloses that rHuAFP expression in *E. coli* is preferred over other expression systems ("for the first time large quantities of pure, homogeneous, functional rAFP will enable systematic study of [the biological function of AFP]"; see page 178, col. 1). Given that a proper reading of Bennett does not guide the skilled artisan towards the claimed invention, Applicants submit that a *prima facie* case of obviousness cannot be established by combining Bennett with Morinaga and Deboer, Clark, or Lubon. *See* MPEP § 2144.05 ("A *prima facie* case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention."). Accordingly, Applicants respectfully submit that the rejection of present claims 1, 3, 5-7, and 10-11 for obviousness over Deboer, Clark, or Lubon in view of Morinaga and Bennett is simply a result of impermissible hindsight reconstruction. For this reason as well, Applicants respectfully request that the rejection of claims 1, 3, 5-7, and 10-11 under 35 U.S.C. § 103(a) for obviousness over Deboer, Clark, or Lubon in view of Morinaga and Bennett should be withdrawn and should not be applied to present claims 1, 6, 7, and 21-24.

## CONCLUSION

Applicants submit that present claims 1, 6, 7, and 21-24 are in condition for allowance, and such action is respectfully requested.

Enclosed is a petition to extend the period for replying for three months, to and including November 23, 2006, and a check for the fee required under 37 C.F.R. § 1.17(a).

If there are any other charges, or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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